Quantum-Mechanical Study of the Conformational Properties of Sympatholytic Compounds

J. L. Coubeils, Ph. Courrière, and B. Pullman*

Institut de Biologie Physico-Chimique, Laboratoire de Biochimie Théorique associé au C. N. R. S., Paris 5è, France.
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Quantum-mechanical calculations have been performed by the molecular orbital PCILO method on the conformational properties of the compound $C_6H_5OCH_2CH_2N^+H_3$ representing the active group of a series of synthetic sympatholytics and of the compounds $C_6H_5NHCH_2CH_2N^+H_3$, $C_6H_5SCH_2CH_2N^+H_3$, and $C_6H_5OCH_2N^+H_3$ representing inactive structures. The results indicate that while the stable conformation of the active compound bears important geometrical analogies to the stable conformation previously reported for α-sympathomimetic catecholamines, this is not so for the inactive compounds. It seems plausible to suggest that the sympatholytic compounds of the type considered here act competitively with sympathomimetic phenethylamines upon the same cellular receptor.

A number of synthetic sympatholytic compounds [*e. g.*, 2-diethylaminomethyl-1,4-benzodioxane, piperoxan (piperidinomethylbenzodioxane), 2-(diethylaminoethoxy)diphenyl, phenoxybenzamine (*N*-phenoxyisopropyl-*N*-benzyl-β-chloroethylamine) etc.,] contain the grouping: $C_6H_5OCHCH_2N<$ considered as their active moiety.[1] In particular the active agents of this type need 2 carbons between the O and N atoms. The activity disappears when only 1 C is present. The activity disappears also when the ester O is replaced by NH or S.[1]

It appeared interesting to us to compute quantum mechanically the conformational energy map and thus to find out the preferred conformational form of the model ion, $C_6H_5OCH_2CH_2N^+H_3$ (I), and to compare the results with the model of the α-sympathomimetic receptor which we have recently proposed on the basis of a similar quantum-mechanical study of a series of substituted phenethylamines.[2] For the sake of additional evidence we have also calculated the 3 model inactive compounds: $C_6H_5NHCH_2CH_2NH_3^+$ (II), $C_6H_5SCH_2CH_2NH_3^+$ (III), and $C_6H_5OCH_2NH_3^+$ (IV). This study does not pretend to give a general theory of sympatholytic activity, its conclusions being necessarily limited to the type of compounds considered here.

Experimental Section

The method utilized in these calculations is, as in ref 2, the PCILO (Perturbative Configuration Interaction using Localized Orbitals) method.[3] Standard values of bond lengths and angles have been utilized as geometrical input data.

The torsion angles taken into account for the construction of the conformational energy maps are indicated in Figure 1. (The torsion angle τ of the bonded atoms A–B–C–D is the angle between the planes ABC and BCD. Viewed from the direction of A, τ is positive for clockwise and negative for counterclockwise rotations (Figure 2). The value $\tau = 0°$ corresponds to the planar-cis arrangement of of the bonds AB and CD.) These include the angles $\tau_1(C_5–C_6–O_7–C_8)$, $\tau_2(C_6–O_7–C_8–C_9)$, and $\tau_3(O_7–C_8–C_{10}–N_{10})$ in I and the corresponding angles with O_7 replaced by N_7 or S_7 in II or III and the angles $\tau_1(C_5–C_6–O_7–C_8)$ and $\tau_2(C_6–O_7–C_8–N_9)$ in IV. In all cases the compounds have been considered in the quatefnary form, known to be essential for their activity and the NH_3^+ group was fixed in a staggered position, following previous results.[1-6]

For each of the compounds I, II, and III, two conformational maps giving the energy as a function of τ_1 and τ_2 have been constructed, for 2 preselected values of τ_3:60° and 180° ($\tau_3 = -60°$ would give results identical to $\tau_3 = 60°$). In each case the 2 maps have been found to be quite similar with the global minimum of the maps corresponding to $\tau_3 = 60°$, however, constantly more stable, by about 3–3.3 kcal/mole, than the minimum of the maps corresponding to $\tau_3 = 180°$. Therefore only the maps corresponding to the preselected value of $\tau_3 = 60°$ are reproduced in this paper for I, II, and III. The rotations about the torsion angles τ_1 and τ_2 were carried out with 30° increments.

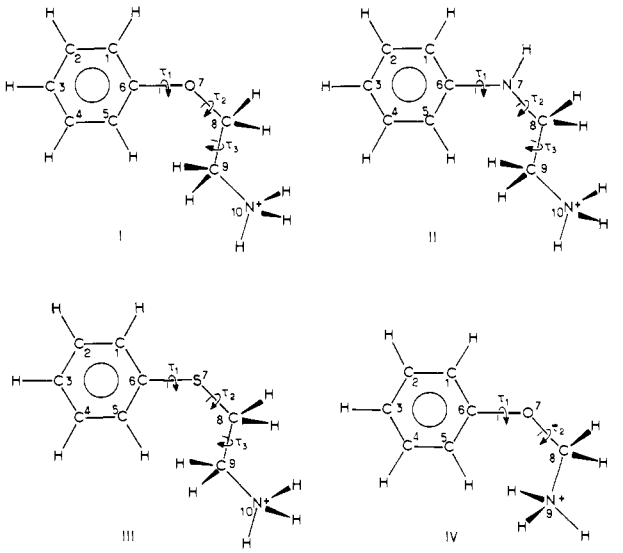


Figure 1. Torsion angles in model compounds I–IV.

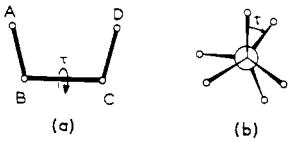


Figure 2. The definition of the torsion angle τ. (a) View perpendicular to the bond. (b) View along the bond (a positive rotation is indicated).

Results

The conformational energy map for the sympatholytic grouping represented by I is given in Figure 3. The results indicate a strong preference for the value of $\tau_2 = 180°$. The global minimum corresponds to $\tau_1 = 0°$ (or 180° which represents the same conformation with the aromatic ring simply turned over by 180°) and $\tau_2 = 180°$. τ_1 may, however, vary from −60° to +30° with the variation of the conformational energy remaining smaller than 1 kcal/mole.

The conformational energy maps of II and III in which the ester O of I is replaced by NH and S are shown in Figures 4 and 5, respectively. Compound II exhibits much less conformational freedom than compound I (or III) owing to the hindering effect of the H atom present on N_7. Its

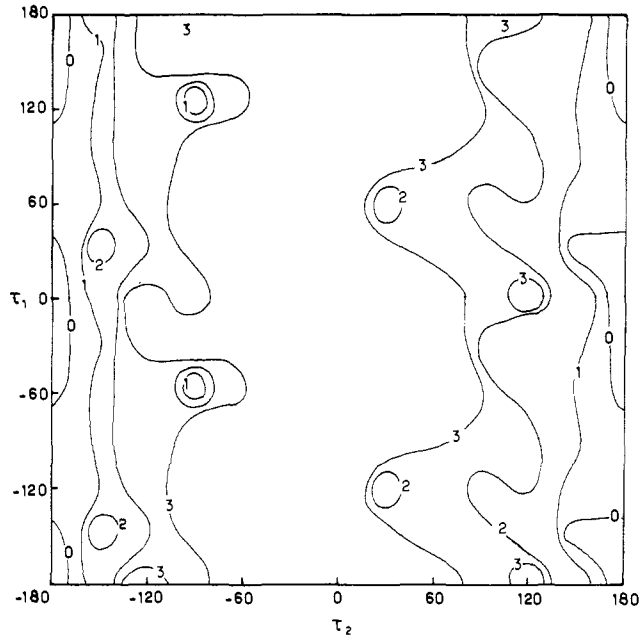


Figure 3. Conformational energy map for I. Isoenergy curves in kcal/mole with respect to the global minimum taken as energy zero.

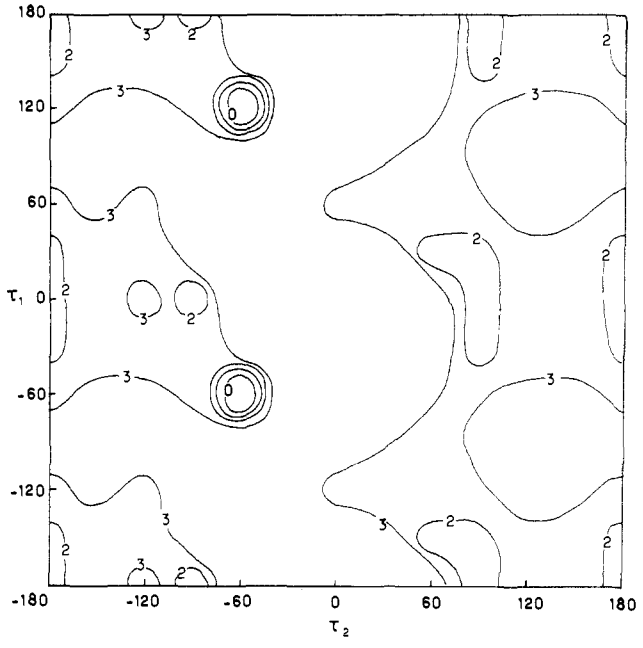


Figure 5. Conformational energy map for III. Isoenergy curves in kcal/mole with respect to the global minimum taken as energy zero.

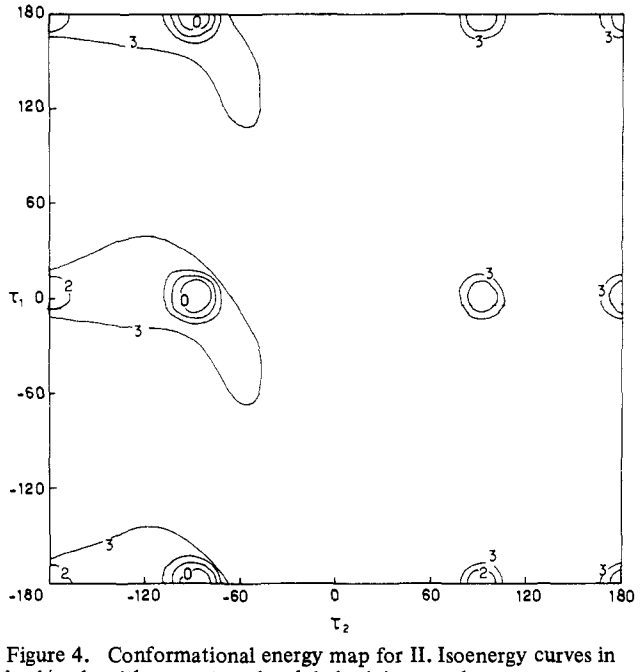


Figure 4. Conformational energy map for II. Isoenergy curves in kcal/mole with respect to the global minimum taken as energy zero.

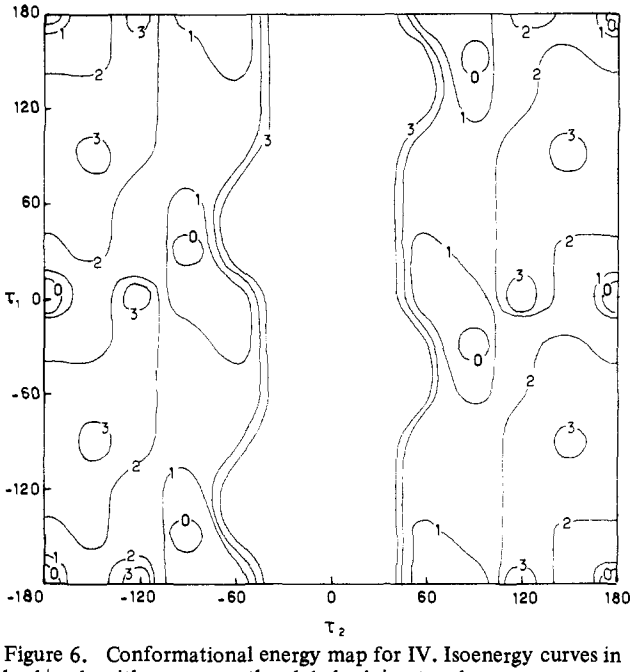


Figure 6. Conformational energy map for IV. Isoenergy curves in kcal/mole with respect to the global minimum taken as energy zero.

global minimum is found for $\tau_1 = 0$ and $\tau_2 = 90°$. Compound III has an allowed conformation space similar in magnitude to that on I but the location of its global minimum is quite different. It corresponds to $\tau_1 = \tau_2 = -60°$.

Finally, the conformation energy map of IV is presented in Figure 6. The available conformational space is large and contains 2 practically equivalent global minima: one at $\tau_1 = 0°$, $\tau_2 = 180°$ and another one at $\tau_1 = 30°$ and $\tau_2 = -90°$.

Discussions and Conclusions

The conformational energy maps and the positions of the global minima are obviously appreciably different for the 4 compounds studied. We have examined the results specifically with respect to the model of the α-sympathomimetic receptor proposed previously on the basis of a similar study of a series of phenethylamines.[2] For this reason we have calculated in particular the distance between the cationic center on N^+ and (1) the center of the aromatic ring and (2) the plane of the aromatic ring. These 2 distances, denoted *D* and *H*, respectively, are indicated in Figure 7 for I (Figure 7a) and compared with the similar distances computed for the α-adrenergic receptor (Figure 7b) in ref 7. Taking into account the uncertainties implied in the calculations (standard bond lengths and angles, 30° increments in τ_1 and τ_2, etc.), it seems evident that the 2 sets of distances are very similar. It seems therefore plausible to admit that the sympatholytic compounds possessing an ac-

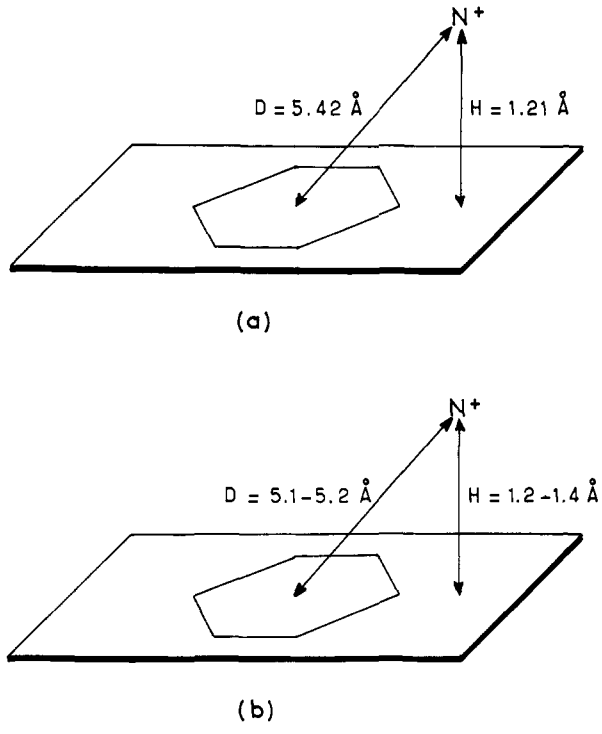


Figure 7. Postulated receptor features in (a) sympatholytic receptor of type I and (b) α-sympathomimetic receptor.

Table I. Distances *D* and *H* (in Å) for the Most Stable Conformations of I-IV.

Compound	Distance *D*	Distance *H*
I	5.42	1.21
II	3.81	2.14
III	3.09	2.60
IV	4.97	0
	4.25	0.42

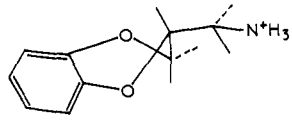
tive grouping of type I act competitively with sympathomimetic catecholamines upon the same cellular receptor. This result confirms Belleau's hypothesis suggesting a gauche conformation for O-C-C-N in phenoxy-β-HEA's[7-10] as well as Portoghese's study on the blocking of the α-adrenergic receptor by phenoxybenzamine.[11]

This conclusion is further substantiated by the results of a similar evaluation of these 2 important distances in II, III, and IV. Their values are indicated in Table I, from which it is evident that they are *very* different for the stable conformations of these compounds from their values in I.

Altogether it seems therefore possible that the sympatholytic compounds of type I act competitively with the sympathomimetics having the quaternary ammonium group and the aromatic ring similarly positioned for the interaction with the receptor. This positioning is quite different in II, III, and IV and forbids such an interaction.

In view of this result the question may be raised as to the exact role of the ester O in I. Because of the inability of IV to act as a sympatholytic, it seems probable that the role of this O in I consists primarily of enabling the appropriate positioning of the N^+H_3 cationic group with respect to the Ph ring rather than of its own specific activity toward the receptor.

Finally, we would like to add that it has been pointed out by a referee that considerable support for our hypothesis derives from several semirigid benzodioxane derivatives[12,13] with α-blocking and sympatholytic properties.



V

These compounds all have the plausible 3-dimensional structure V from which one can easily find *via* models that $\tau_1 = -150°$, $\tau_2 = 180°$, and τ_3 is probably 60°, a point very close to the global minimum found for I.

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